REMARKS/ARGUMENTS

I. Specification

The abstract of the disclosure stands objected to for allegedly containing more than 150 words. The abstract, as presently amended, contains 136 words. No new matter is added by way of the amendment to the abstract.

The USPTO requires that the Applicants to submit sequence listings. The present amendments insert the Sequence Listing into the specification. No new matter is added by way of the paper copy of the Sequence Listing.

The disclosure stands objected to for allegedly containing embedded hyperlink. The present amendments contain no hyperlinks. No new matter is added by way of the removal of the hyperlinks.

The specification stands objected to for failure to provide antecedent basis for the limitations "discriminating *de novo* sequence" and "non-discriminating sequences" in Claims 65, 67, 70, and 71. The present amendments to the claims are believed to provide sufficient antecedent basis for said limitations in the claims.

II. Claims

A. No new matter is added by the amendments.

The present amendments to the claims find support in the specification and claims as originally filed. For example:

Claim 1 as currently amended contains the limitation "fragment" in line 3. This limitation is supported by paragraph 0023 in the original specification.

Claims 1, 76, and 82, as currently amended, contain step of storing the result on a computer readable medium. This step is supported by the recitation "XML result files facilitate automatically adding the methods and systems of the present invention alignments into a relational database" in paragraph 0043 of the original specification.

Claim 5, as currently amended, recites "ambiguous mass regions" of molecules. This amendment is supported by paragraph 0023 in the original specification.

Claim 37, as currently amended, recites the generation of a new local mass-based alignment after all fragments are matched in a breadth-first search. This amendment is supported by paragraph 0051 in the original specification.

Claim 39, as currently amended, recites the identification of modification sites. The identification of modification sites is supported by, *e.g.,* paragraph 0027 in the original specification.

B. Claim objections

Claims 72 and 81 stand objected to for alleged improper multiple dependency. Claims 72 and 81 are currently amended to overcome this objection.

Claims 1, 13, 29, 31, 40, 42, 52, 69, 70, 76, and 82 stand objected to for alleged informalities. Said claims are currently amended to overcome the objections.

C. The Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 1-71, 76, 82-84 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Particularly:

Claims 1-71, 76, 82-84 stand rejected for allegedly being indefinite for the limitations "molecules in each sequence," "sequence of molecules," and similar terminology. Said claims are currently amended to overcome the rejection by reciting "fragment" or "fragments" in places of "molecule" and "molecules," respectively. These amendments are believed to be sufficient to overcome the instant rejection.

Claims 65, 67, 70, and 71 stand rejected for alleged indefiniteness for the limitations "discriminating *de novo* sequences" and "non-discriminating *de novo* sequences." Further, the Examiner relied on the specification for the definition of a "delta score." Said claims are currently amended such that terms "discriminating *de novo* sequences" and "non-discriminating *de novo* sequences" are defined in Claim 67, as amended. Also, the definition of a "delta score" is currently provided in Claim 65. The support for this definition is in paragraph 0049 in the original specification. These amendments are believed to be sufficient to overcome the instant rejection.

Claims 1 and 82 stand rejected for alleged insufficient antecedent bases for the limitation "the sequence in the sequence database" and "the *de novo* sequence." Claims 1 and 82 are currently amended to provide bases for each of the said limitations.

Claims 12, 13, 19, 27, 32, 33, 34, 38, 46-48, 56, 58, 59, 63, and 64 stand rejected for alleged insufficient antecedent basis for the limitation "the sequence in the sequence database." Said claims are claims ultimately dependent on Claim 1. Claim 1, as currently amended, recites "a sequence in the sequence database." This recital provides sufficient antecedent basis for the limitations and is believed to overcome the rejection.

Claims 19, 27, 33, 47, 48, 58, and 60-64 stand rejected for alleged insufficient antecedent basis for the limitation "the *de novo* sequence." Said claims are claims ultimately dependent on Claim 1. Claim 1, as currently amended, recites "a *de novo* sequence." This recital provides sufficient antecedent basis for the limitations and is believed to overcome the rejection.

Claim 28 stands rejected for alleged insufficient antecedent basis for the limitation "the next specified number." Claim 28 is currently amended to use the limitation "a specified number." The support for this amendment is in paragraph 0035 in the original specification, where the specified number is three (3). This amendment is believed to be sufficient to overcome the instant rejection.

Claims 31 and 32 stand rejected for alleged insufficient antecedent basis for the limitation "the breadth first search." Claims 31 and 32 are currently amended to use "a breadth-first search" and "said breadth-first search," respectively. The support for this amendment is in, e.g., paragraph 0035 in the original specification. These amendments are believed to be sufficient to overcome the instant rejection.

Claim 37 stands rejected for alleged insufficient antecedent basis for the limitations "the next molecule in the *de novo* sequence" and "the next molecule in the sequence in the sequence database." Claim 37 as currently amended recites the generation of a new local mass-based alignment after all fragments are matched in a breadth-first search. This amendment is supported by paragraph 0051 in the original

specification. No new matter is added. This amendment is believed to be sufficient to overcome the instant rejection.

Claims 41-45 stand rejected for alleged insufficient antecedent basis for the limitations "the modification information," "the modification," and "the modification site." Said claims are currently amended to overcome the instant rejection.

Claim 48 stand rejected for alleged insufficient antecedent basis for the limitation "the mass-based alignment." Claim 48 is currently amended to overcome the instant rejection.

Claims 66 and 68 stand rejected for alleged insufficient antecedent basis for the limitation "the *de novo* sequence." Said claims are dependent on Claim 65. Claim 65, as currently amended, recites "a *de novo* sequence." This recital provides sufficient antecedent basis for the limitations and is believed to overcome the rejection.

Claim 67 stands rejected for alleged insufficient antecedent basis for the limitation "the delta score threshold." Claim 67, as currently amended, recites "a delta score threshold." The support for this limitation is in paragraph 0043. "[V]arious intermediate score multipliers and score thresholds can be adjusted." This amendment is believed to be sufficient to overcome the instant rejection.

Applicants respectfully submit that Claims 1, 65, 67, 70, 71, and 82 are not indefinite as currently amended. Applicants further respectfully submit that Claims 1, 12, 13, 19, 27, 28, 31-34, 37, 38, 41, 42, 44-48, 56-64, 66-68, and 82 have sufficient bases for the limitations therein as currently amended. Accordingly, Applicants respectfully submit that the rejections of said claims under 35 U.S.C. §112, second paragraph, are overcome.

D. The Rejections under 35 U.S.C. § 101

Claims 1-71, 76, and 82-84 stand rejected for allegedly directing to non-statutory subject matter. Claims 1, 76 and 82, as currently amended, produces tangible results and are therefore believed to be directed to statutory subject matter. For example, Claims 1, 76, and 82, as currently amended, include the step of storing the result on

computer readable medium. Said step is supported in the original specification in paragraph 0043.

III. The Rejections under 35 U.S.C. §103(a)

The Examiner rejected Claims 1-12, 63-71, 76 and 82-84 under §103(a) as being unpatentable over Dancik *et al.* (Journal of Computational Biology, 1999, volume 6, pp. 327-342) in view of Pevzner *et al.* (Genome Research, 2001, volume 11, pp. 290-299).

Applicants respectfully disagree and traverse the rejection.

To reject claims in an application under 35 U.S.C. §103, the PTO bears the initial burden of establishing a *prima facie* case of obviousness. *In re Bell*, 26 USPQ2d 1529, 1530 (Fed. Cir. 1993); M.P.E.P. §2142. In order to establish *prima facie* obviousness, three basic criteria must be met. First, the prior art must provide one of ordinary skill in the art with a suggestion or motivation to modify or combine the teachings of the references relied upon by the PTO to arrive at the claimed invention. Second, the prior art must provide one of ordinary skill in the art with a reasonable expectation of success that the modification or combination suggested by the PTO would succeed. *In re Dow*, 5 USPQ2d 1529, 1531-32 (Fed. Cir. 1988). (Emphasis added). Third, the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. *In re Gartside*, 53 USPQ2d 1769 (Fed. Cir. 2000). If any one of these criteria are not met, *prima facie* obviousness is not established, and Applicants are not required to show new or unanticipated results. *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985). Furthermore, M.P.E.P. §2142 states, "The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

Applicants submit that Dancik *et al.* teach a method for the identification of de novo sequences using a tandem mass spectrometer and Pevzner *et al.* teach methods drawn to efficient database searching for identification of mutated and modified proteins via mass spectroscopy. Nevertheless, contrary to the Examiner's assertion, Dancik *et*

al. in view of Pevzner *et al.* do not disclose each and every limitation encompassed by the independent Claims 1 or 82, nor those claims dependent thereupon. Specifically, the cited references when taken alone or in any combination, do not teach or suggest the following steps in Claim 1 of the instant application which discloses a method for identifying a macromolecule and sequence modifications thereof from mass spectrometry data:

c) interpreting mass differences between the sequence in the sequence database and the *de novo* sequence using a modification catalog, said mass differences having been identified within said mass-based alignment,

(f) grouping identifications of sequences in the sequence database from at least one *de novo* sequence into an identified macromolecule list that agrees with the *de novo* sequencing results.

While acknowledging that Dancik et al. does not fairly teach or suggest interpreting mass differences of modification as disclosed in step (c) of Claim 1, the Examiner asserts that Pevzner et al. "sets forth methods drawn to efficient database searching for identification of mutated and modified proteins via mass spectrometry." (Page 17 of the instant Office Action).

Applicants submit that there would be no reasonable expectation of success based on the cited references. Pevzner *et al.* do not teach the identification of modifications using a modification catalog, but instead teach a mutation/modification – "tolerant" method that "reliably identifies peptides differing by up to two mutations/modifications from a peptide database." (Page 290, Abstract). That is, they are able to identify peptide matches in a database in spite of the presence of a mutation/modification in a peptide. However, Applicants would like to further point out that the Pevzner technique involves matching ion series in MS/MS spectra to peptide sequences without using a stringent parent ion mass filter. This approach comes with a tradeoff in the accuracy of its scoring function that often assigns high scores to incorrect peptide identification by chance (page 298, column 1, paragraph 2), thereby limiting its

application in high-throughput environments, such as described in the instant specification.

The Examiner further alleges that "Figure 1 and Table 1 of Pevzner et al list a plurality [of] modified peptides used in the disclosed methods and is fairly interpreted to read on a modification catalog as instantly claimed." (Page 18 of the instant Office Action).

Applicants submit that the modification catalog referred to in the instant application is used as a means to identify ambiguous mass differences between the sequence in the sequence database and the *de novo* sequence. Neither Figure 1 nor Table 1 adequately disclose information for this purpose. The three hypothetical spectra of peptides depicted in Figure 1 would represent an extremely limited and ultimately insufficient database of mutation containing peptides. The peptides listed in Table 1 of Pevzner et al are merely an accounting of the sample peptides matched against the yeast protein database using their disclosed algorithms. Therefore, Applicants submit that Pevzner does not disclose a meaningful modification catalog for interpreting mass differences between a de novo sequence and a sequence in a sequence database identified by mass-match alignment.

The Examiner also asserts that Pevzner et al.'s application of the spectral convolution algorithm allows for the detection of mutations/modifications without an exhaustive search. (Page 18 of the instant Office Action).

Applicants submit that the method of Pevzner *et al.* for detecting mutations/modifications is not equivalent to **interpreting** mass differences and **identifying** the specific modifications as disclosed in the instant application. Relating to the identification of peptides, as described in Pevzner, the instant specification teaches "[i]n one embodiment of the present invention, mass-based alignment of *de novo* sequences are utilized to accurately identify sequence variations and post-translational protein modifications, thus allowing for these types of searches to succeed in a high-throughput environment." (Paragraph [0043]). This paragraph of the instant specification goes on to state that the identification of these modifications will be useful

in constructing relational databases for "cataloging of protein sequence variations and sites of post-translational modifications."

Finally, Applicants reiterate that neither Pevzner nor Dancik teach methods for assembling identified peptides for the purpose of accurately identifying the macromolecule as disclosed in step (f) of Claim 1 which discloses grouping identifications of sequences in the sequence database from at least one *de novo* sequence into an identified macromolecule list that agrees with the *de novo* sequencing results. Accordingly, the instant claims are not obvious over Dancik *et al.* in view of Pevzner *et al.* Applicants respectfully request withdrawal of the present rejection.

The examiner has rejected Claims 1-27, 63-71, 76 and 82-84 under §103(a) as allegedly being unpatentable over Dancik *et al.* in view of Pevzner *et al.* and further in view of Mann *et al.* (Analytical Chemistry, 1994, volume 66, pp. 4390-4399).

As discussed above, Dancik *et al.* in view of Pevzner *et al.* do not disclose each and every limitation of Claims 1 or 82, nor those claims dependent thereupon, for at least the reasons given above. Mann *et al.* do not cure the deficiencies of Dancik *et al.* in view of Pevzner *et al.*, as Mann *et al.* do not teach methods for: 1) interpreting mass differences between the sequence in the sequence database and the *de novo* sequence using a modification catalog, said mass differences having been identified within said mass-based alignment, or 2) grouping identifications of sequences in the sequence database from at least one *de novo* sequence into an identified macromolecule list that agrees with the *de novo* sequencing results.

The Examiner asserts that Mann et al. sets forth methods for "interpreting complex tandem mass spectra by use of searching by peptide sequence tags." (Page 19 of the instant Office Action).

Applicants submit that Claims 13-27 of the instant application, which specifically disclose the tag match method, ultimately depend from Claim 1. As Mann *et al.* do not disclose each and every limitation of Claim 1, these claims are also not anticipated by Mann *et al.*

The Examiner further alleges that Mann et al. "demonstrate that MS/MS data can be relied upon for peptide identification with tags as short as two amino acids that can further be located in the presence of posttranscriptional modification or a sequence difference between the measured peptide and the peptide database." (Pages 19-20 of the instant Office Action).

Applicants submit that while Mann *et al.* discusses a method for identifying peptides "even in the presence of an unknown posttranslational modification or an amino acid substitution between an entry in the sequence database and the measured peptide" (Page 4390, abstract), the method of Mann *et al.* does not seek to locate or identify modification sites. In fact, Mann *et al.* specifically teach away from this step, stating "[i]t may, however, only be possible to locate the modification to within several amino acids if the required fragment ions are missing from the tandem mass spectrum." (Page 4397, column 2, paragraph 1). Applicants further point out that Mann *et al.* provide no information about the limitations and error rates of this approach, but subsequent adaptations of the sequence tag method have indicated a tendency to assign high scores to incorrect matches when attempting to identify modified peptides (see Pappin *et al.* and Tabb *et al.*, previously made of record).

Applicants respectfully submit that there would be no reasonable expectation of success based on the cited references. The cited references when taken alone or in any combination, do not teach or suggest method for identifying a macromolecule having a sequence and sequence modifications thereof from mass spectrometry data following the steps recited in the claims. Accordingly, since the instant claims are not obvious over Dancik *et al.* in view of Pevzner *et al.* and further in view of Mann *et al..*, Applicants respectfully request withdrawal of present rejection.

The Examiner has rejected Claims 1-71, 76 and 82-84 under §103(a) as being unpatentable over Dancik *et al.* in view of Pevzner *et al.* in view of Mann *et al.* and further in view of Bader (Bioinformatics, 2003, volume 19, pp. 1869-1874).

As discussed above, Dancik *et al.* in view of Pevzner *et al.* and further in view of Mann *et al.* do not disclose each and every limitation of Claim 1 and 82 or those claims

dependent thereupon. Bader *et al.* do not cure the deficiencies of Dancik *et al.*, Pevzner *et al.* and Mann *et al*, as Bader *et al.* do not teach a method for identifying a macromolecule having a sequence and sequence modifications thereof from mass spectrometry data following the steps recited in the claims of the instant application.

The Examiner alleges that Bader et al. teach "the evaluation of the disclosed algorithm by use of a breadth-first outward search based on an outward traversal of a protein interaction network." (Page 21 of the instant Office Action).

Applicants note that the relevance of the Bader reference is unclear. Bader describes the development of an algorithm, SEEDY, that extracts biologically relevant networks from protein-protein interaction data, building out from selected seed proteins. (page 1869, abstract). While Bader does in a single instance refer to an algorithm based on a breadth-first application (page 1870, column 2, paragraph 3), the author states "The higher AUC value indicates that confidence scores provide a significant improvement for algorithms based on breadth-first outward traversal of a protein interaction network." This statement is unrelated to the methods disclosed in the instant application.

As discussed above, Applicants respectfully submit that there would be no reasonable expectation of success based on the cited references. The cited references when taken alone or in any combination, do not teach or suggest methods for identifying sequences of molecules and sequence modifications from mass spectroscopy data following the steps recited in the claims. Thus, contrary to the Examiner's assertion, Applicants respectfully submit that one skilled in the art would <u>not</u> find the instant application obvious from the teachings disclosed in the cited references. Accordingly, since instant claims are not obvious over Dancik *et al.* in view of Pevzner *et al.* in view of Mann *et al.* and further in view of Bader, Applicants respectfully request withdrawal of present rejection.

CONCLUSION

Applicants respectfully submit that Claims 1 though 84 are in condition for allowance, and respectfully request their reconsideration and allowance. Early notification of the allowance of the application is respectfully requested.

The Examiner is invited to contact the undersigned attorney at the telephone number indicated below should he find that there are any further issues outstanding.

Fees for three months' extension of time are believed to be due. Please charge any fees, including the fees for extension of time, or credit overpayment to Deposit Account No. **08-1641** referencing Attorney's Docket No. **39767-0003**.

Respectfully submitted,

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By: _____
Paul Davis (Reg. No. 29,294)

HELLER EHRMAN LLP
275 Middlefield Road
Menlo Park, California 94025
Direct Dial: (650) 324-6951
Telephone: (650) 324-7000
Facsimile: (650) 324-6654

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